Response to Role of Epithelial Sodium Channels in the Renal Myogenic Response?

Loutzenhiser and Aaronson argue that a lack of effect of amiloride and benzamil at 1 μmol/L suggests that “[epithelial sodium channels] ENaC plays little if any role in myogenic signaling” in the afferent arteriole. They are correct. However, we do not hypothesize that the classical “ENaC channel” (formed by αβγENaC) is acting as a vascular mechanosensor. We hypothesize the proteins that form ENaC channels (ie, βENaC and γENaC) in epithelial cells associate with related acid-sensing ion channel (ASIC) proteins to form a mechanosensor, a very important distinction. We have used the Caenorhabditis elegans mechanosensor as a mammalian vascular mechanosensor because ENaC proteins are related to proteins that form the pore of the C elegans mechanosensor. In this model, the mechanosensor is formed by an ion channel (ENaC-ASIC), which is tethered and gated by interactions with extracellular matrix and cytoskeleton proteins.

Because of a scarcity of approaches to silence vascular degenerins, broad-spectrum ENaC-ASIC inhibitors, such as amiloride, have been used initially to determine the importance of ENaC proteins as mediators of the myogenic response. Because of the predicted heteromeric nature of the mechanosensor and the potential influence of electrochemical gradient, protein modification, and splice variants on amiloride sensitivity, we did not expect the amiloride sensitivity of the myogenic response to match precisely with those of channels formed by αβγENaC proteins in expression systems and native epithelia. Thus, differences in amiloride specificity are expected because the vascular mechanosensor is not the classical ENaC channel.

Loutzenhiser and Aaronson also suggest that, “Direct electrophysiological approaches may ultimately resolve this issue and determine whether a channel with the functional and pharmacological properties of ENaC is observed in afferent arteriole myocytes.” Although it would be convenient to find an ENaC channel in vascular smooth muscle cells by electrophysiology, failure to find such a channel does not necessarily mean that ENaC proteins are not functional in vascular smooth muscle cells. C elegans literature suggests that the wild-type degenerin mechanosensor model is electrically silent. Thus, an ENaC-containing mechanosensor is likely to be electrically silent. Then the question becomes whether the channel is gated. If the extracellular matrix is critical to gating the mechanosensor, as the model predicts, then preparing vascular smooth muscle cells for electrophysiological assessment by enzymatic dissociation destroys the extracellular matrix essential to gating. Thus, an electrically silent channel and no gating mechanism could easily explain the absence of electrophysiological evidence for the ENaC channel.

Evidence for ENaC protein function will likely require the use of genetically modified animals. Progress in determining the importance of ENaC and ASIC proteins to myogenic responsiveness in genetically modified animals is underway. Recent studies indicate that mice with reduced levels of βENaC have altered myogenic responsiveness and blood flow autoregulation. Although these studies suggest a role for ENaC/ASIC proteins in mediating myogenic constriction, more studies are needed to understand the role and physiological importance of ENaC/ASIC proteins in the kidney and other organs.

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Disclosures

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